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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/599,594
Filing Date: June 22, 2000
Appellant(s): NAZARENKO ET AL.

Frank R. Cottingham
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 5, 2006 appealing from the Office action mailed January 4, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment after final rejection filed on September 5, 2006 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,465,175	HORN	10-2002
6,037,130	TYAGI	03-2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 12, 14, 15, 17-19, 59 and 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn et al (U.S. Patent 6,465,175) in view of Tyagi et al (U.S. Patent 6,037,130).

Horn teaches a method of claims 11 and 12 for quantification of target nucleic acid molecules in a sample comprising:

(a) Mixing one or more target nucleic acid molecules with one or more fluorescently labeled oligonucleotides (see column 3, lines 7-20),

Wherein said one or more oligonucleotides are labeled with only a single type of detectable label, said single type of detectable label having the same chemical structure (see column 3, lines 7-20, where only a single label is used)

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 3, lines 7-20, where the label is fluorescent when the probe is single stranded by is quenched when hybridized). In particular, Horn shows in example 1 at columns 13 and 14, that the BODIPY FL label was capable of being quenched by hybridization when it was directly linked to the probe, but not when it was linked via a linker which rendered it distant from the hybridization. In example 3 at columns 15 and 16 and in figure 1, Horn shows quenching with multiple labels with the same chemical structure, that of BODIPY FL. Horn makes the use of a single label explicit in example 5, where a modified Taqman assay is taught in which an oligonucleotide singly labeled with BODIPY FL is used without the use of a quencher dye (see column 17, lines 50-55).

(b) Incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to a portion of said one or more target nucleic acid molecules (see columns 17 and 18)

(c) detecting the presence or absence or quantifying the amount of the target molecules by measuring the fluorescent label (see columns 17 and 18).

With regard to claims 14, 15, Horn teaches measurement of the fluorescence during PCR (see column 17, example 5), during LCR (see example 7, column 18) and during SDA (see example 9, column 19).

With regard to claims 17, 19, 59, Horn teaches the use of hairpin oligonucleotides (see figure 4, panel B, for example).

With regard to claim 18, Horn teaches appliication of the method to PCR (see column 2, line 55, for example).

With regard to claims 66, 67, Horn teaches placing the dye at the 3' termini (see column 13, line 39).

Horn expressly teaches application of the method to the use of hairpins and expressly references using Tyagi type molecular beacons with a single fluorescent bodipy label (see columns 17 and 18, example 6).

Horn does not teach incorporation of the hairpin primer into the PCR product and Horn does not teach each possible location of the internal base.

Tyagi teaches the use of hairpin primers (see column 18, example 5) and expressly teaches the use of fluorescently labeled molecular beacon primers being incorporated into the PCR product (see column 18, example 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the single label method of Horn

with the hairpin primers of Tyagi since Horn notes "When used in nucleic acid amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube. See, Tyagi et al. (1996) Nature 14:303-308 (see column 18, lines 4-7)." Further motivation to use the modify the Tyagi primers to use a single label is present when Horn notes "Accordingly, single label quenching molecular beacons can be used for the detection of nucleic acids in homogeneous assays and in living cells, as well as for real time monitoring of assays in which nucleic acids are being synthesized, e.g., polymerase chain reactions (see column 18, lines 43-47)." So an ordinary practitioner is motivated to substitute the single label quenching beacons of Horn in the method of Tyagi so that a separate quenching dye is not necessary (see column 18, line 32). Further, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

Allowable Subject Matter

Claims 78-79 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: In the absence of any evidence, the ordinary practitioner would expect that all fluorescent labels would function equally well in this assay. However, Horn specifically teaches that "Extensive quenching was observed with the BODIPY FL-labeled oligomer, in contrast to the fluorescein- and Texas Red-labeled oligomers which did not show an noticeable quenching under the same hybridization conditions (see column 14, lines 23-27)." In contrast, Applicant's specification expressly shows that each of the claimed labels, including fluorescein and rhodamine, function in the assay. Given direct experimental evidence demonstrated by Applicant, opposed by just a negative teaching of Horn that is not supported by data, the claims are found to be enabled. However, the negative teaching by Horn qualifies under MPEP 2145 as a direct teaching away from the use of these labels. Consequently, there is no case of prima facie obviousness due to the express teaching away of the Horn reference for use of fluorescein and Texas-red type labels, and no reasonable expectation that other labels would therefore function in the claimed assay. For these reasons, the indicated claims drawn to the specific labels, are objected to as discussed above.

(10) Response to Argument

Issue

Would it have been prima facie obvious to utilize the singly labeled oligonucleotide primer taught by Horn as functional in a PCR based Taqman assay in other prior art assays such as the PCR assay of Tyagi in which the primer is incorporated into the amplified product?

Prima Facie case

The prima facie case of obviousness in this application is based upon a primary reference which teaches a nearly identical method to that method claimed, with the secondary reference teaching and motivating an alternative means of performing the assay. Comparing the claim limitations with the Horn patent, where PCR is a method of nucleic acid synthesis,

Claim 11	Horn et al (U.S. Patent 6,465,175)
A method for the quantitation or detection of one or more target nucleic acid molecules in a sample during nucleic acid synthesis	"The present invention provides methods and probes for detecting nucleic acid analytes in a sample. In general, the methods represent nucleic acid hybridization assays, such as fluorescent in situ hybridization assays, polymerase chain reaction assays ..." (see column 2, lines 52-56)

Mixing one or more target nucleic acid molecules with one or more fluorescently labeled oligonucleotides, wherein said one or more oligonucleotides are labeled with only a single type of detectable label, said single type of detectable label having the same chemical structure, and said one or more labels undergo a detectable change in an observable property upon said hybridizing	"The method comprises (a) providing an oligonucleotide probe comprising (i) a nucleic acid sequence complementary to a nucleic acid sequence in the oligonucleotide of interest, and (ii) a label that, when the probe is in single-stranded, nonhybridized form, provides a detectable fluorescent signal, but which, when the probe hybridizes to a complementary nucleic acid strand, does not fluoresce (see column 3, lines 7-14), Also see column 18, lines 30-39
Incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to all or a portion of said one or more target nucleic acid molecules	"Incorporation of quenchable dye-labeled nucleotide triphosphates during enzymatic DNA/RNA synthesis produces a strongly fluorescent oligomer. However, the dye will be quenched when the oligomer is in a double- or triple-stranded hybrid complex. (see column 19, lines 9-16, also see column 17, example 8)

detecting the presence or absence or quantifying the amount of the target molecules by measuring the fluorescent label.	"correlating any decrease in fluorescence which occurs throughout step (b) with the presence or quantity of the oligonucleotide of interest. (see column 3, lines 18-20 or claim 1, step c)."

The only element missing from the Horn reference is found in the final element of the second step, "said one or more synthesized nucleic acid molecules comprising said one or more oligonucleotides". This element requires that the singly labeled oligonucleotide function as a primer in the amplification reaction. While Horn does teach incorporation of labeled nucleotides into amplification reactions (as in example 8) and Horn also teaches incorporation of primers into amplification reactions (see example 5) and of course Horn teaches singly labeled primers for detection throughout the patent (see column 3, lines 7-14, for example), Horn does not teach incorporation of the singly labeled primer into the amplification reaction.

Tyagi teaches the use of hairpin primers in an identical method to that of Horn's and the claims, differing only in the use of doubly labeled primers instead of singly labeled primers (see column 18, example 5). Tyagi expressly teaches the use of fluorescently labeled molecular beacon primers being incorporated into the PCR product (see column 18, example 5). Tyagi expressly notes "As stated earlier, a wavelength-shifting molecular beacon probe whose 3' arm

sequence is complementary to the target can serve as a primer (see column 18, lines 32-34)."

Tyagi then expressly teaches how to take oligonucleotides which were designed to function as probes, just like the oligonucleotides of Horn that are primarily used as probes, and modify these oligonucleotide probes so that they will function as oligonucleotide primers in a polymerase chain reaction amplification reaction, where the primers will be incorporated into the amplification reaction (see column 18, line 32 to column 19, line 16 of Tyagi).

The two references, Horn and Tyagi, relied upon for the prima facie case of obviousness, teach and suggest all of the limitations of the claims.

Motivation

The crux of the issue is whether there is motivation to modify the singly fluorescent labeled probes of Horn to function as primers in an amplification assay, as Tyagi modified the older prior art doubly labeled probes to function as primers in an amplification assay.

Two specific motivations were identified in the rejection. The first motivation is based on the express statement of Horn. Horn notes "Accordingly, single label quenching molecular beacons can be used for the detection of nucleic acids in homogeneous assays and in living cells, as well as for real time monitoring of assays in which nucleic acids are being synthesized, e.g., polymerase chain reactions (see column 18, lines 43-47)." While Horn is referring to Taqman type assays in this quote, it is clear that Horn is

contemplating the use of the single label molecular beacons in polymerase chain reactions.

A second and independent motivation derives from the teaching of Horn that his method is an improvement over the prior art (such as Tyagi) in that "This same design can be used without the need for a separate quenching dye (see column 18, lines 31-32)." This directly suggests to the ordinary practitioner, performing the extension method of Tyagi using the double labeled primer, that the single labeled primer of Horn will function. Motivations to use a single label results include Horn's statement that the singly labeled probes "nucleic acid hybridization assays having reduced background noise by, for example, producing a detectable signal only upon dissociation of a directly labeled probe from its complement are a significant improvement over conventional assay methods. (see column 10, lines 6-10)." An ordinary practitioner would be motivated to use singly labeled probes to reduce background noise as well as based upon reduced cost since only a single label will need to be purchased and used in the oligonucleotide synthesis.

Appellant argues that Tyagi uses probes which are labeled with two fluorophores rather than one fluorophore and that this use of two fluorophores teaches away from the use of one fluorophore. To the contrary, Tyagi was unaware of the advance of Horn that a single fluorophore could be used in the place of two fluorophores (which occurred subsequent to Tyagi) and Tyagi simply teaches the basic method of amplification using the labeled oligonucleotide as a primer.

As the Federal Circuit noted in In re Fulton, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004), "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed in the '198 application. Indeed, in the case cited by appellants, In re Gurley, we held that the invention claimed in the patent application was unpatentable based primarily on a prior art reference that disclosed two alternatives, one of which was the claimed alternative. Accordingly, mere disclosure of alternative designs does not teach away." In the current case, the disclosure by Tyagi of an earlier design does not teach away from the improved design using a single label taught by Horn in the subsequent art.

Appellant then argues that the combination of the references would not yield the claimed invention. This argument is simply not correct because it fails to combine the references in the way that the ordinary artisan would be motivated to combine. The ordinary artisan would not modify the primer of Tyagi by removing a quenching dye, but would rather substitute the entire primer of Horn for the primer of Tyagi. That is, in the amplification reaction of Tyagi, the ordinary practitioner would be motivated to use the new and improved single label oligonucleotide of Horn in the place of the doubly labeled oligonucleotide of Tyagi for the reasons given above.

In fact, Horn expressly teaches that the singly labeled probe would function as a replacement for the double labeled probe of Tyagi in example 6, where a different Tyagi method using double labeled probe is discussed and

Horn indicates that the single labeled probe can be used in the place of Tyagi's double labeled probe.

Appellant then argues that Horn is focused on probes and does not teach the use of these probes as primers. That is correct and is the reason that Horn is not an anticipatory reference instead of a reference in a prima facie obviousness rejection. It is Tyagi who teaches the oligonucleotides which are used as probes may also be used as primers, as Tyagi notes "As stated earlier, a wavelength-shifting molecular beacon probe whose 3' arm sequence is complementary to the target can serve as a primer (see column 18, lines 32-34)." The evidence to fulfil the deficiency argued by Appellant is found in Tyagi, who teaches that probes can also function as primers.

Reasonable Expectation of Success

Appellant then argues this there is no reasonable expectation of success in the combination. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)."

In this case, there is express suggestion in Horn to use the singly labeled oligonucleotides in prior art assays (see column 11, lines 56-61 and all of the examples). In fact, Horn expressly teaches that the singly labeled probe can function in the place of Tyagi's double labeled probe in a different assay taught

by Tyagi in a different prior art paper (see example 6, where Tyagi's doubly labeled probe is replaced by Horn's singly labeled probe).. This sufficient for a reasonable expectation of success in replacing the doubly labeled oligonucleotide of Tyagi in the amplification reaction with the singly labeled probe of Horn. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a

variety of parameters, since the Horn directly points to the use of the single labeled probes in the place of double labeled probes and even expressly teaches replacement in a different Tyagi assay. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of substituting probes as primers, where Tyagi notes "As stated earlier, a wavelength-shifting molecular beacon probe whose 3' arm sequence is complementary to the target can serve as a primer (see column 18, lines 32-34)."

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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PRIMARY EXAMINER
10/5/06

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